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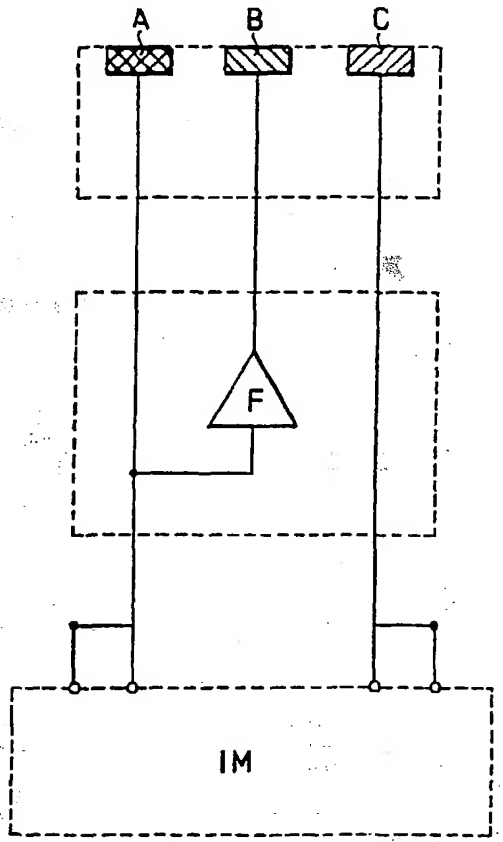
(54) Title: A DEVICE FOR MEASUREMENT OF ELECTRICAL IMPEDANCE OF ORGANIC AND BIOLOGICAL MATERIALS

(57) Abstract

A device for depth-selective, non-invasive, local measurement of electrical impedance of organic and biological materials such as tissues from vegetable or animal origin comprising a probe (Fig. 1-3, 9a, 9b) with a number of electrodes (A, B, C) driven from an electronic control unit (F), in such a way that the electric current path defining the actual tissue under test is dependent upon a control signal. The probe is pressed toward the surface of the body part under test and by varying the control signal, it is possible to select the region under test within limits determined by the shapes, sizes and distances of the electrodes and the properties of the tissue under test. By means of combining results obtained with different control signals, it is possible to compute local impedance profiles.



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A DEVICE FOR MEASUREMENT OF ELECTRICAL IMPEDANCE OF ORGANIC AND BIOLOGICAL MATERIALS.

BACKGROUND OF THE INVENTION

The present invention relates to a device for non-invasive depth-selective detection and characterization of surface phenomena in organic and biological systems such as tissues by surface measurement of the electrical impedance of said material with said device as well as a method for said surface characterization.

Electrical impedance is a very sensitive indicator of minute changes in organic and biological material and especially tissues such as mucous membranes, skin and integuments of organs, including changes due to irritation caused by different reactions, and scientists all over the world have worked hard to find a convenient way to measure variations and alterations in different kinds of organic and biological material to be able to establish the occurrence of such alterations

which are due to different states, characteristic of irritations from e.g. diseases.

Much of the fundamental knowledge within the current area stems from the field of electrochemistry. Potentiostats have for a long time been in use for studies of e.g. corrosion, and AC (alternating current) methods have gradually evolved and are well documented, cf. Claude Gabrielli: Identification of electrochemical processes by frequency response analysis. Solartron Instruments technical report number 004/83, 1984 and F.B. Growcock: What's impedance spectroscopy. Chemtech, september 1989, pp 564-572.

Excellent tools for work in this field are available, e.g. the 1286 Electrochemical Interface, Solartron Instruments, UK and the Model 378 Electrochemical Impedance Systems, EG&G Princeton Applied Research, NJ, USA.

Characteristic features of these systems are that they are intended for use with specimens mounted in appropriate electrochemical cells.

It is well known that certain parameters in living tissues are reflected by electrical impedance of said tissues: U.S.P. 4,038,975 (Aug. 2,1977) to Vrana et al. relates to an electrically instrumented method of diagnosing the presence of a neoplast in mucuos membrane samples wherein the electrical impedance of the sample has resistive and capacitive compo-

nents and wherein the relative values of said components are indicative of the presence or absence of said neoplast by associating the sample with the terminals of a series circuit including in succession a grounded, amplitude-modulated high-frequency generator and first and second equal-valued resistors wherein the impedance of the generator and the resistance of both resistors are low relative to the impedance of the sample. Said association being made by connecting a test spot on the sample to the terminal of the second resistor remote from the junction of the first and second resistors and by connecting the bulk of the sample to the grounded terminal of the generator, simultaneously measuring the amplitudes of the potentials of the test spot and of the junction of the first and second resistors with respect to a reference value established at the junction of the generator and the first resistor, and computing from the measured values and from the reference value the resistive and capacitive portions of the impedance of the test spot.

By EP 0 315 854 (Appln. No. 88118083.0) to Honna is previously known a method and a system for measuring moisture content in skin by passing "weak" low frequency electric current through the keratinous layer between two electrodes abutted upon the skin, amplifying the electric voltage appearing on the layer, rectifying and taking out signals of the amplified output, and measuring the amplitude of the signal, which is characterized in that the voltage appearing on the keratinous layer is the voltage appearing between either one of said two electrodes

whichever is closer to another electrode which is abutted upon said skin at a location outside said two electrodes.

The system comprises a measuring electrode structure of triple concentric circles including a central electrode, an intermediate electrode and an outer electrode all of which can be abutted on the skin, a generator which uses one of said electrodes as a common electrode and supplies low frequency signal between this common electrode and another of said three electrodes; an amplifier which converts the resulting current into a voltage appearing between said common electrode and yet another of said three electrodes, and a means to display the output voltage of the amplifier which is characterized in that a circuit means is provided for switching between a first circuit using said intermediate electrode as common electrode and a second circuit which uses the outer electrode as a common electrode.

Further prior art is disclosed in e.g. Yamamoto, T. & Yamamoto, Y.: Analysis for the change of skin impedance. Med. & Biol. Eng. & Comp., 1977, 15, 219-227; Salter, D.C.: Quantifying skin disease and healing *in vivo* using electrical impedance measurements. In: Non-invasive physiological measurements, Vol 1, 1979, Peter Rolfe ed., pp 21-64; Leveque, J.L. & De Rigal, J.: Impedance methods for studying skin moisturization. J.Soc.Cosmet.Chem., 1983, 34, 419-428; and Morkrid, L. & Qiao, Z.-G.: Continuous estimation of parameters in skin electrical admittance from simultaneous measurements at two

different frequencies. Med. & Biol. Eng. & Comp., 1988, 26, 633-640.

Characteristic of existing technology in this field is that either: a) a biopsy would have to be excised in order to well define the actual tissue under test, i.e. not suitable for in vivo measurements; or

b) electrodes are applied to the skin at separate sites, directing the electric test current right through the skin and regarding the inner part of the skin and deeper lying tissue as an almost ideal short circuit between the contact sites, i.e. no discrimination between the layers of the rather complicated anatomy of the skin.

There are devices for measuring the water content in the outermost layers of the skin (such as the Corneometer CM820PC, Courage + Khazaka Electronic GmbH, FRG) using interdigitated electrode patterns. A device called DPM9003 from NOVA Technology Corporation, Mass., USA employs a simple coaxial electrode. These devices have no means for controlling the measurement depth except for the limitations set by physical size. Indeed, they are applications of the well known principle of moisture measurement using fringing fields (Giles: Electronic sensing devices, Newnes, London, 1966/68, pp 80-81).

A device for measuring conductance of the fluids in mucous

membranes of the airways has been published (Fouke, J M et al: Sensor for measuring surface fluid conductivity in vivo. IEEE Trans. Biomed. Eng., 1988, Vol 35, No 10, pp 877-881). This paper shows, backwards, the problem encountered while measuring on wet surfaces without a control electrode to enforce depth penetration.

It is possible to use Applied Potential Tomography/Electrical Impedance Tomography to obtain tomographic images of e.g. thorax or gastric regions, employing a large number of electrodes around the body and computing with reconstruction algorithms an image representing changes of conductivity in the body (Seagar, A.D. & Brown, B.H.: Limitations in hardware design in impedance imaging. Clin. Phys. Physiol. Meas., 1987, Vol. 8, Suppl. A, 85-90).

According to the present invention depth selectivity is achieved by controlling the extension of the electric field in the vicinity of the measuring electrodes by means of a control electrode between the measuring electrodes, the control electrode being actively driven with the same frequency as the measuring electrodes to a signal level, taken from one of the measuring electrodes but also multiplied by a complex number, in which the real and imaginary parts are optimized for each application depending upon the desired depth penetration. The function of the controlling field is analogous to that of a field effect transistor, well known from solid state physics. In biological tissue or "wet state", conduction

mechanisms are complicated involving a number of ions, polarization effects, charged or polarizable organelles, etc. However, no reconstruction algorithms are needed to achieve depth selectivity, although consecutive measurements at different depths must be recorded in order to obtain a profile.

The principle is basically frequency independent, and works from DC to several MHz. Simple impedance measurements at one or a few frequencies, as well as impedance spectroscopy in this range can thus be done depth selective on e.g. skin.

In mucous membranes the fluid on the surface would normally short circuit measuring electrodes placed on the same surface; however, by use of the control electrode the test current is forced down into the mucous membrane rather than taking the shortest way and local definition of the actual tissue under test is thus achieved. These advantages are directely applicable while measuring impedance as an indicator of irritation during tests of irritants on skin and oral mucous membranes. It was also possible to measure impedance on kidneys while at the same time measuring the blood pressure within the kidney in the main artery, and it was found that impedance descriptive parameters correlated well with blood pressure. This opens the possibility to measure pressure, as well as microcirculation non-invasively in many organs during surgery by applying a probe to the surface of the organ. Another application is the measuring of pressure in the eye (diagnosis of glaucoma).

SHORT DESCRIPTION OF THE DRAWINGS.

Fig. 1 is a block diagram illustrating the principle of measurement employed in an embodiment of the present invention;

Fig. 2a is a plane topview of the tip of a probe with two measuring electrodes separated by a control electrode;

Fig. 2b is a cross-sectional view along plane S - S of Fig. 2a;

Fig. 3a is a cross-sectional view of a probe with linear, iterated structure;

Fig. 3b is a perspective view of the tip of the probe with a linear, iterated structure, electrically equvivalent to Fig. 3a;

Fig. 3c is a perspective view of the tip of a simplified structure of a similar arrangement, sufficient in some applications.

Fig. 4a is an illustration of a normal tissue with closed packed cells;

Fig. 4b is an illustration of an irritated tissue showing increased intercellular space;

Fig. 5 is a plot showing mean values in % obtained with prior technique in measurement of irritation on oral mucosa for NaCl, H_3PO_4, SLS;

Fig. 6 is a plot showing values in % for one person obtained with the technique according to the invention in the measurement of irritation on oral mucosa;

Fig. 7 is a plot showing irritation index results of measurement of irritation on skin with the technique according to the invention for one person with 20 hours of exposure of material and additionally 24 hours;

Fig. 8 is a plot showing absolute value of electrical impedance at 20 kHz measured on intact surface of rat kidney at consecutive values of blood pressure by stepwise choking and releasing supporting artery in vivo;

Fig. 9a is a plane topview of a generalized probe switchable into different configurations;

Fig. 9b is a cross-sectional view along plane S - S of Fig. 9a showing also switchable electrical pathways.

DESCRIPTION

The essential features of the invention are a probe with two measuring electrodes separated by a control electrode, suitable equipment for measuring the electric impedance in the

desired frequency range, and an amplifier with adjustable amplification capable of maintaining the chosen control signal, derived from the potential of one of the measuring electrodes at the control electrode without loading said measuring electrode, i.e. the amplifier must have high input impedance and low output impedance in the frequency range used. The control electrode is following the potential of one of the measuring electrodes by multiplying the signal of the amplifier with a complex number in which the real and imaginary parts are optimized for each application. With the amplification factor set to zero, the system assumes the special case of signal ground at the control electrode. In this special case the system behaviour is similar to the system in the prime case of Fig. 1 described in the EP Publication No. 0 315 854 (Application No. 88118083.0), where one electrode is always connected to signal ground. However, the intermediate electrode of said system is not actively driven by an amplifier as in the present invention but is galvanically connected to signal ground. According to the present invention any control signal different from zero (the amplitude may be less than, equal to, or larger than the amplitude supplied to the measuring electrodes) will modify the depth penetration within a range determined by the shapes, sizes and distances of the electrodes and the properties of the tissue under test. The present amplifier of course can also be set to signal ground whereby the function signalwise corresponds to the previously known apparatus. However, said feature is outside the scope of the present invention.

The electrodes may be configured in concentric, linear, iterated linear or any topological way compatible with the essential features. Additional electrodes carrying guard, signal ground, driven guard, etc. may be required to optimize operation depending on the application. Cabling and shielding must be in accordance with established engineering practice in order to minimize electromagnetic interference. For use on humans, design may have to conform to local safety regulations.

It is important to limit excitation amplitude in order to minimize non-linearities inherent in living tissues. The amplitude supplied to the electrodes should be no more than a few tens of millivolts, preferably below 50 millivolts and more preferably about 25 millivolt. Higher amplitudes produce unreliable results. Working on wet mucous membranes does not require any special preparations. If deeper layers of the skin (stratum corneum and down) are to be investigated, the dry surface of the skin is preferably inundated with a salt solution of physiological concentration.

The capability of the control electrode to vary depth penetration is, as stated above, limited by the shapes, sizes and distances of the electrodes as well as the properties of the tissue under test. For a large range of depths a variety of probes of different sizes may thus seem necessary. However, a generalized probe can be achieved by adding a number of electrodes which are switched into different functions

according to Fig. 9b. The dominating factor determining depth penetration is distances between electrodes; the basic theory has been expanded by Roy et al (Roy, A. & Apparao, A.: Depth of investigation in direct current methods. Geophysics, Vol. 36, No. 5, 1971, pp 943-959; Roy, K.K. & Rao, K.P.: Limiting depth of detection in line electrode systems. Geophysical Prospecting, 25. 1977, pp 758-767) for a number of electrode configurations.

It is, of course, still essential that the path of the measured test current is kept from the immediate surface of the probe by driving the virtual control electrode according to the present invention. When choosing a certain pair of measurement electrodes, i.e. the center electrode and the most distant of the activated rings, all (minimum one) electrodes in between are connected together to form the virtual control electrode. Distances between electrodes may be the same or vary in a non-linear way to achieve e.g. stepwise increase of penetration with a fixed factor. With the generalized probe coarse depth penetration is thus selected by switching electrodes of the probe, and fine adjustment of penetration as well as facilitating measurements on wet surfaces are achieved by driving the virtual control electrode to the proper potential. The switches may be mechanical or electronic and may be manually operated or under computer control.

For achieving maximum penetration depth, the best mode is thus to use the center electrode and outermost ring as measurement

electrodes and using the rings in between, connected together, as a control electrode, and driving this virtual control electrode with a potential derived from the potential of one of the measurement electrodes in the same way as described above.

If the application is such that optimum results would come from a lesser depth penetration, the best most would be to use another ring as one of the measurement electrodes, leaving the outer ring or rings unconnected and using the ring or rings between the outer electrode and selected second electrode, connected together, as the control electrode.

PREFERRED EMBODIMENT

In Fig. 1 is shown a block diagram illustrating the principle of measurement employed in a preferred embodiment of the present invention. Two measuring electrodes A and C are separated by a third electrode, the control electrode B. Said control electrode B will be actively held at a given potential by a controllable amplifier F, said amplifier F also receiving an input reference signal from electrode A using a high impedance input terminal and supplying said control electrode B via a low impedance output terminal so that said control electrode B will track said electrode A but with a signal level ensueing from the transfer function of the amplifier F. Said measuring electrodes A and C are connected to a standard instrument for impedance measurement IM.

Fig. 2a and Fig. 2b illustrates a preferred embodiment of the tip end of a measurement probe for studies of irritation on i.e. oral mucosa and skin. Said probe consists of the electrodes A, B and C, each electrically isolated from the other, in a coaxial arrangement and presents as depicted in Fig 2a. a plane surface containing respective electrodes A, B and C and the isolating material 1.

Fig. 3b and Fig. 3c are showing the respective embodiments of an open linear, iterated structure which can be used according to the invention. The structure of Fig. 3c involves a simplified feature, within the scope of the invention sufficient in some applications.

The invention relates to a device for depth-selective, non-invasive, local measurement of electric impedance in tissues such as preferably skin, mucous membranes and integuments of organs in or from humans or animals in vivo or in vitro comprising a probe with concentric electrodes, the size of which is depending upon desired maximum depth penetration. The electrodes comprise a central electrode being one of two measuring electrodes, and the central electrode being surrounded by a control electrode which is following the potential of the central electrode by multiplying the signal of one of the measuring electrodes by a complex number in which the real and imaginary parts are optimized for each application. The control electrode is surrounded by a second measuring electrode. The essential part of the probe, except

for the contact surface, is surrounded by conductive material at signal ground or following the potential at the central electrode by a factor of one. All conductive parts are separated by stable isolating material and all electrodes and isolating material on the contact surface arranged in one plane, concave or convex surface to fit the surface of the test site with minimum liquid wedge. The device is further provided with suitable equipment for measuring impedance at a limited number of frequencies, these frequencies determined in pretests for a certain application by a wide scan of frequencies and plotting of Nyquist or Bode graphs.

For measurement of irritation, impedance values at two frequencies, one in the range several hundred kHz to several Mhz, and one in the range 1 kHz to 100 kHz, will work. The major information comes with the lower frequency, the impedance at the higher frequency is used to normalize the geometrical definition of the tissue under test. For convenience, an irritation index defined as the quotient between the absolute value at 20 kHz and the absolute value at 1 MHz has been introduced. Phase is not included in this irritation index. See Fig 4: SIMPLE IRRITATION MODEL. A decrease in irritation index means increased irritation.

For depth selectivity the signal of the control electrode is optimized when the real part is a number between 0.01 - 10 and the imaginary part as close to zero as possible for the transfer function of the amplifier F in the used frequency

range.

APPLICATIONS

SIMPLE IRRITATION MODEL, FIG. 4

Fig. 4a shows normal tissue with close packed cells.

Fig. 4b shows irritated tissue with increased intercellular space.

High frequency (HF) is coupled capacitively through cell membrane to cell interior.

Low frequency (LF) is confined to extracellular/intercellular space.

Conductivity is essentially the same in intra- och extracellular liquid.

IRRITATION ON ORAL MUCOSA, FIG. 5.

Prior Technology

Ten voluntary test persons were exposed to three different liquid substances (sodium chloride, sodium lauryl sulphate and phosphoric acid). Exposure time was 5 minutes for NaCl and H_3PO_4 (-5 to 0 in graph) and 10 minutes for SLS (however plotted between -5 and 0 in graph, for uniformity of nominal value). Electrical impedance was measured through the cheek, with a small electrode on the inside of the cheek at the site of irritation, and a large electrode on the outside of the cheek, thus creating a conical field yielding highest electric current density at the inside. Impedance information is

thus dominated by events at the inside, however somewhat occluded by artifacts occurring in intercepted regions of muscular tissue and skin. Not suitable for diagnostic purposes, since averages from a number of test persons are necessary to obtain significant results.

With said method impedance from the skin of the cheek as well as muscular layers are involved, and averages of data from ten or more test persons are required to see any significant changes, i.e. said prior method is not suitable for diagnostic purposes, and indeed not many mucous membranes are available from two sides non-invasibly.

IRRITATION ON ORAL MUCOSA, FIG. 6.

According to the invention

By the measurement according to the invention artifacts from muscular tissue and skin are eliminated, since the device measures to a controlled depth of the oral mucosa. The results are stable and it is easy to follow the course of events on one single person, i.e. the method is well suited for diagnostic purposes. The graph shows result from 30 minutes exposure (-30 to 0 in graph) to sodium lauryl sulphate, with a pause of approximately 15 seconds half way (at -15 in graph) to measure that point. After 12 hours irritation index is back at normal levels. Maximum irritation of this substance on this test person was reached 15 minutes after cessation of exposure.

With the device according to the invention it is possible to

measure non-invasibly from the surface of any mucous membrane which can be reached from one side. In the case of oral mucosa, artifacts from skin or muscular tissue are eliminated, and it is possible to follow irritation processes on single persons with high accuracy.

IRRITATION ON SKIN, FIG. 7.

According to the invention

Voluntary test persons were exposed to patch test on back. Sodium lauryl sulphate of different concentrations was applied for 24 hours in Finn chambers. Irritation was measured according to the invention and assessed according to standard procedures by a trained dermatologist (scale 0..3, interior labels in graph). There is good correlation between irritation index and concentration for all concentrations, despite the fact that the trained dermatologist could not discern any irritation at the lower concentrations (marked 0 in the graph). With the claimed invention it was possible to detect irritation effects not visible to a trained dermatologist (points marked 0 in FIG 7).

PRESSURE IN KIDNEY IN VIVO, FIG. 8.

According to the invention

Absolute value of electrical impedance at 20 kHz was measured on the intact surface of a rat kidney, still in function. At the same time arterial pressure was measured with a sensor implanted in the supporting vessel. Consecutive blood pressures were induced by choking and releasing the supporting

artery. Impedance correlated well with pressure, with a delay of approximately 15 seconds. Graph shows sequence of events. Autoregulatory mechanisms of the kidney are not demonstrated explicitly with this type of plot.

The device according to the invention has been tried for measurement of electric impedance on intact kidney of rat in vivo, the kidney being exposed to changes in blood circulation and pressure. There is significant correlation between pressure and value of measured impedance, the correlation being higher at 20 kHz (FIG 8) than at 100 kHz. Thus, the device according to the invention may be useful to detect ischemic states during e.g. transplantational surgery.

As the behaviour of the eye seems similar to the kidney when it comes to tissue changes in the surface due to internal pressure, the invention may be useful for diagnosis of glaucoma.

CLAIMS

1. A device for depth-selective measurement of electrical impedance of organic and biological material comprising a probe with measuring electrodes separated by a control electrode, an equipment for measuring of electric impedance and an amplifier, c h a r a c t e r i z e d in that in the probe, the control electrode is supplied via the amplifier with a signal taken from one of the measuring electrodes without loading of the measuring electrode, i.e. by a high input impedance, and an output impedance of the amplifier low enough, and the power of the amplifier strong enough, to maintain the desired dynamic potential of the control electrode for all conceivable properties under test.

2. The device according to claim 1, c h a r a c t e r i z e d in that the frequence response of the amplifier is wide enough not to introduce conceivable phase or amplitude errors in the output signal.

3. The device according to claim 1, c h a r a c t e r i z e d in that the amplitude to the electrodes are below a few tens of millivolt, preferably below 50 millivolt and more preferably about 25 millivolt.

4. The device according to claim 1, c h a r a c t e r i z e d in that the transfer function of the amplifier is externally

controllable.

5. The device according to claim 1, 3 and 4, c h a r a c t e r i z e d in that the externally controllable transfer function of the amplifier is manually selectable or continuously variable.

6. The device according to claim 1 and 3-5, c h a r a c t e r i z e d in that the amplifier is stepwise or continuously controlled by the measuring system.

7. The device according to claim 1, c h a r a c t e r i z e d in that the potential of the control electrode is following the potential of one of the measuring electrodes by multiplying the signal at said measuring electrode with an adjustable amplifier by a complex number, in which the real and imaginary parts are optimized for each application, and feeding the control electrode from said amplifier.

8. The device according to claim 1, c h a r a c t e r i z e d in that the contact surface at the end of the probe, containing the measuring and control electrodes, and the isolating material between said electrodes and the tissue, independent of the form, are in the same surface level in order to minimize the remaining liquid layer in between the probe and the test site whereby the control electrode facilitates a deeper penetration than the thickness of the remaining liquid layer.

9. The device according to claim 1, c h a r a c t e r i z e d in that for measurement of irritation impedance values at two frequencies are used.

10. The device according to claim 1 and 9, c h a r a c t e - r i z e d in that for measurement of irritation one frequence in the range several hundred kHz to several MHz and one in the range 1kHz to 100 kHz, is used; the higher frequency to normalize the geometrical definition of the tissue under test.

11. The device according to claim 1 and 7, c h a r a c t e - r i z e d in that for measurement of irritation the signal of the control electrode is optimized when the real part is a number between 0.01 - 10 depending on chosen depth penetration and the imaginary part is as close to zero as possible in the used frequency range.

12. The device according to claim 1, c h a r a c t e r i z e d in that it is provided with an equipment for measuring impedance at limited number of frequencies, said frequencies determined in pretests.

13. The device according to claim 1, c h a r a c t e r i z e d in that it is provided with additional electrodes carrying guard, signal ground, driven guard etc., cabling and optionally adequate shielding.

14. A probe for measuring of electrical impedance comprising concentric or topologically equivalent arrangements of electrodes in which measuring electrodes are separated by a control electrode, the distance between the measuring electrodes corresponding to desired maximum depth penetration, one of the measuring electrodes being a central electrode, and said central electrode surrounded by a control electrode, and the control electrode surrounded by a second measuring electrode; the potential of the control electrode is following the potential of the central electrode or the second measuring electrode by multiplying said potential in an adjustable amplifier by a complex number in which the real and imaginary parts are optimized for each application; the essential part of the probe, except for contact surface, is surrounded by conductive material at signal ground or following the potential at the central electrode by a factor of one, and all conductive parts separated by stable isolating material and all electrodes and isolating material on the contact surface arranged in one plane, concave or convex surface to fit the surface of the test site with minimum liquid wedge.

15. A method for depth-selective, non-invasive surface characterization of organic or biological material, c h a r a c t e r i z e d in that the impedance of organic or biological materials is measured from the surface of said material by application of a device as defined in claims 1 and 7.

16. The method according to claim 15, c h a r a c t e r i z-e d in that the impedance due to irritation effects or other changes in the organic or biological material such as e.g. skin or mucous membranes or other integuments is measured.

17. The method according to claim 16, c h a r a c t e r i z-e d in that the impedance due to irritation effects or other changes in the kidneys or the eye is measured.

18. A generalized probe, c h a r a c t e r i z e d in that coarse depth penetration is achieved by switching electrodes into different functions, and fine adjustment as well as possibility to measure on wet surfaces are achieved by driving the virtual control electrode to the proper potential.

AMENDED CLAIMS

[received by the International Bureau on 16 March 1992 (16.03.92); original claim 15 amended; other claims unchanged (2 pages)]

14. A probe for measuring of electrical impedance comprising concentric or topologically equivalent arrangements of electrodes in which measuring electrodes are separated by a control electrode, the distance between the measuring electrodes corresponding to desired maximum depth penetration, one of the measuring electrodes being a central electrode, and said central electrode surrounded by a control electrode, and the control electrode surrounded by a second measuring electrode; the potential of the control electrode is following the potential of the central electrode or the second measuring electrode by multiplying said potential in an adjustable amplifier by a complex number in which the real and imaginary parts are optimized for each application; the essential part of the probe, except for contact surface, is surrounded by conductive material at signal ground or following the potential at the central electrode by a factor of one, and all conductive parts separated by stable isolating material and all electrodes and isolating material on the contact surface arranged in one plane, concave or convex surface to fit the surface of the test site with minimum liquid wedge.

15. A generalized probe according to claim 1, c h a r a c t e r i z e d in that the control electrode is replaced by a number of electrodes which are switched into function as control electrode or measuring electrode according to the desired physical size of the active probe area and that coarse

depth penetration is achieved by switching the electrodes into different functions, and that fine adjustment as well as a possibility to measure on wet surfaces are achieved by driving the virtual control electrode to the proper potential.

16. A method for depth-selective, non-invasive surface characterization of organic or biological material, c h a r a c t e r i z e d in that the impedance of organic or biological materials is measured from the surface of said material by application of a device as defined in claims 1 and 7.

17. A method according to claim 15, c h a r a c t e r i z e d in that the impedance due to irritation effects or other changes in the organic or biological material such as e.g. skin or mucous membranes or other integuments is measured.

18. The metod according to claim 16, c h a r a c t e r i z e d in that the impedance due to irritation effects or other changes in the kidney or the eye is measured.

STATEMENT UNDER ARTICLE 19

The new claim 15 as filed is amended in that a reference to claim 1 is added together with information from page 11, line 7 from the bottom to page 13, line 11, from fig 9 a and b as well as from the original claim 18. Nothing in the amendments goes beyond the disclosure in the International Application as filed.

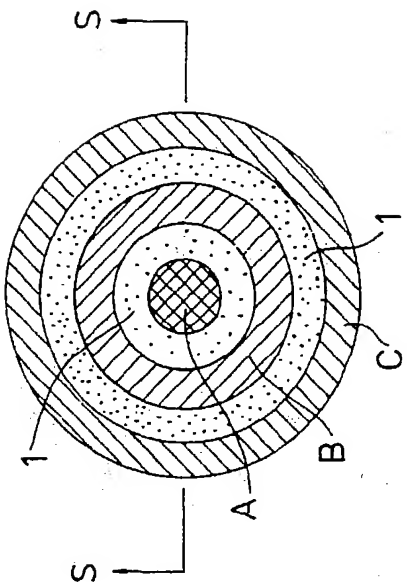


Fig. 2a

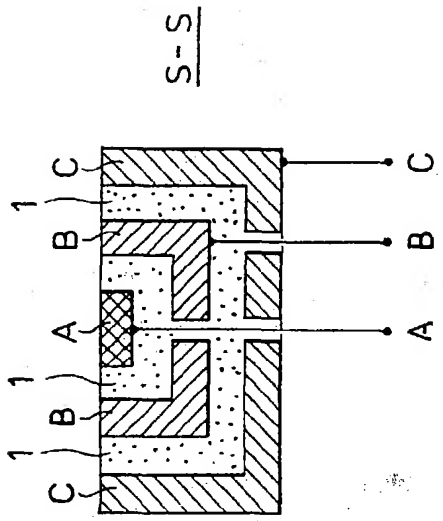


Fig. 2b

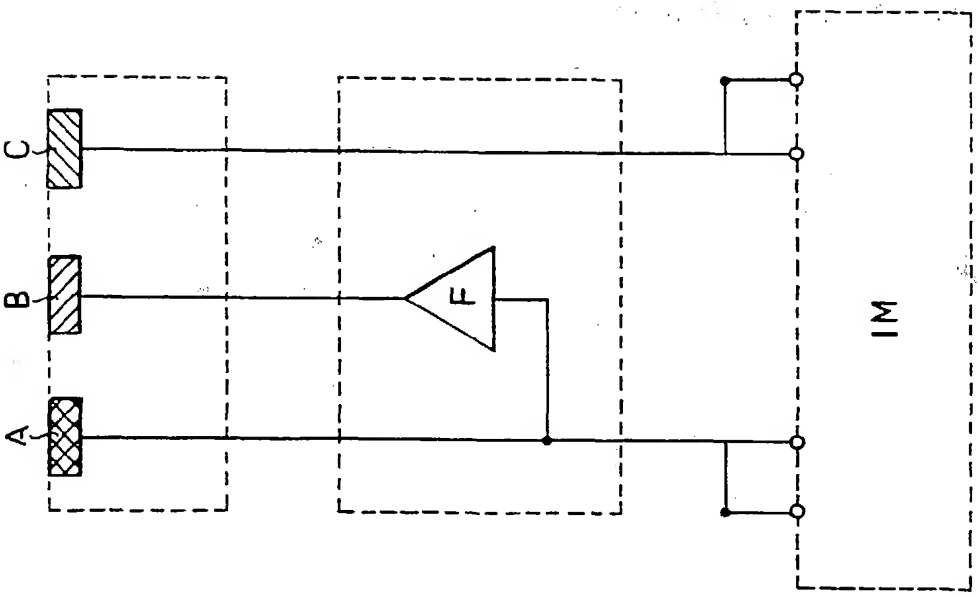


Fig. 1

Fig. 3a

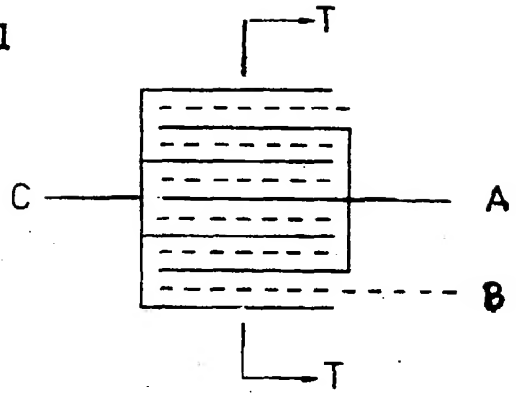
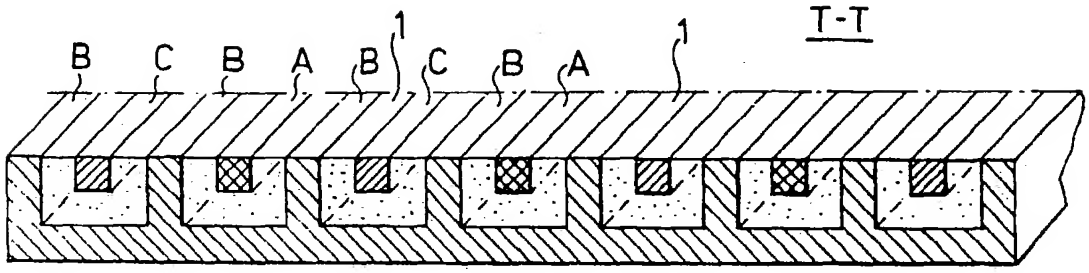


Fig. 3b



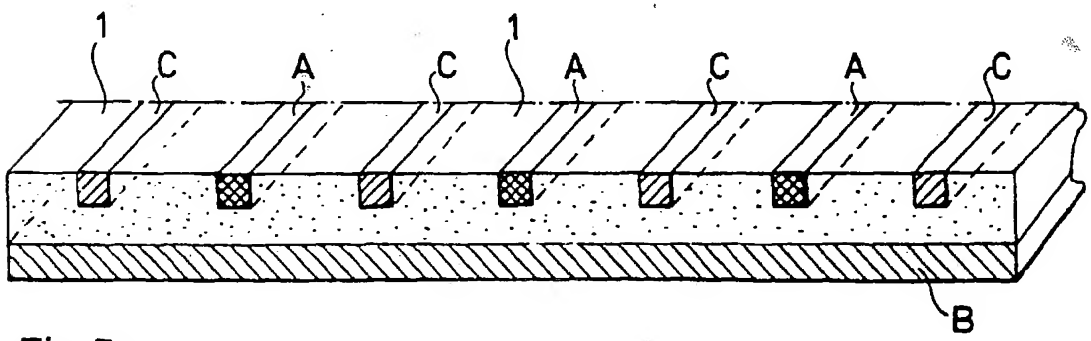


Fig. 3c

Fig. 4a

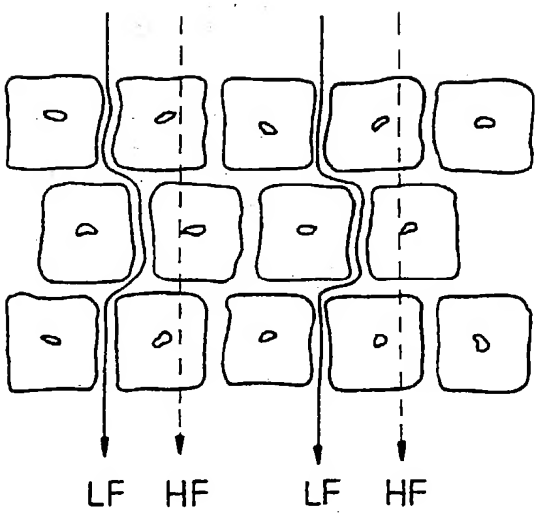


Fig. 4b

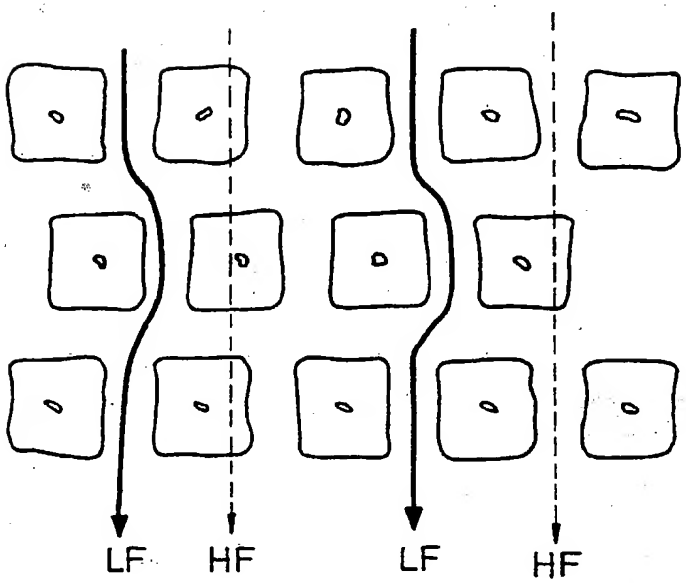
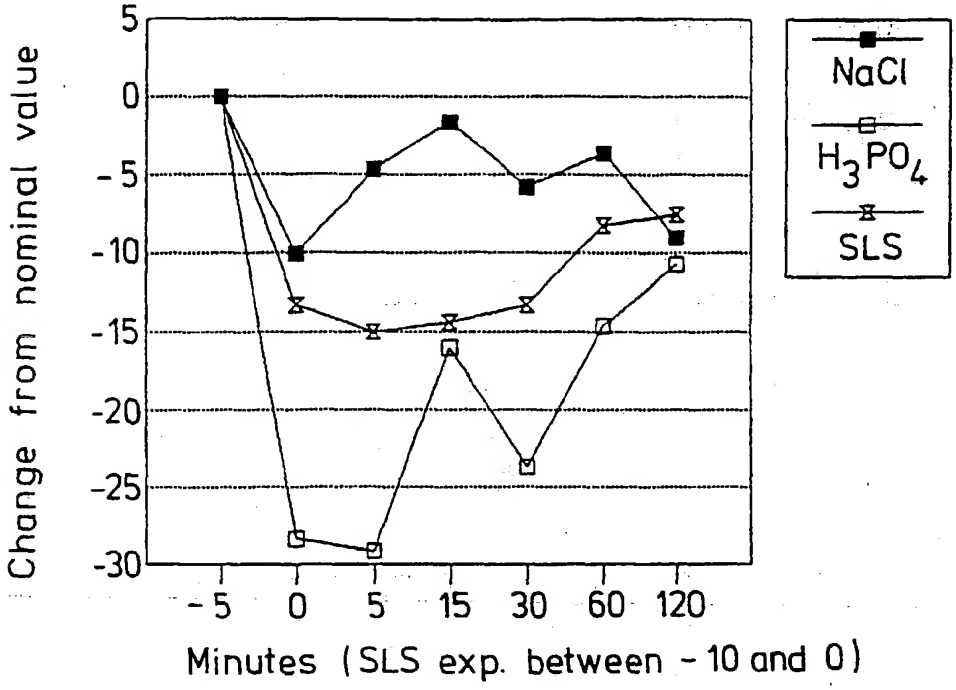


Fig. 5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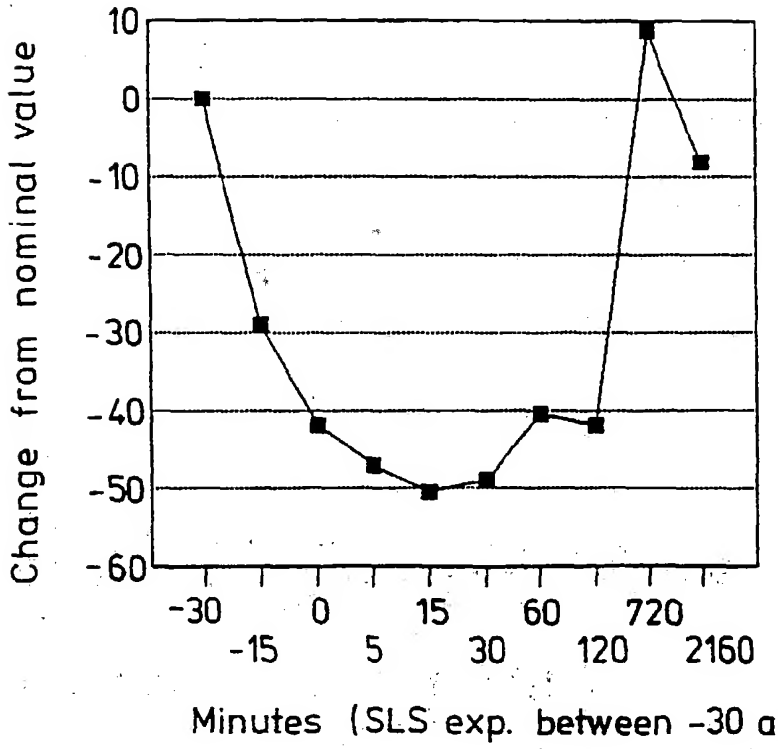
Minutes (SLS exp. between -10 and 0)
NaCl
H_3PO_4
SLS

Fig. 6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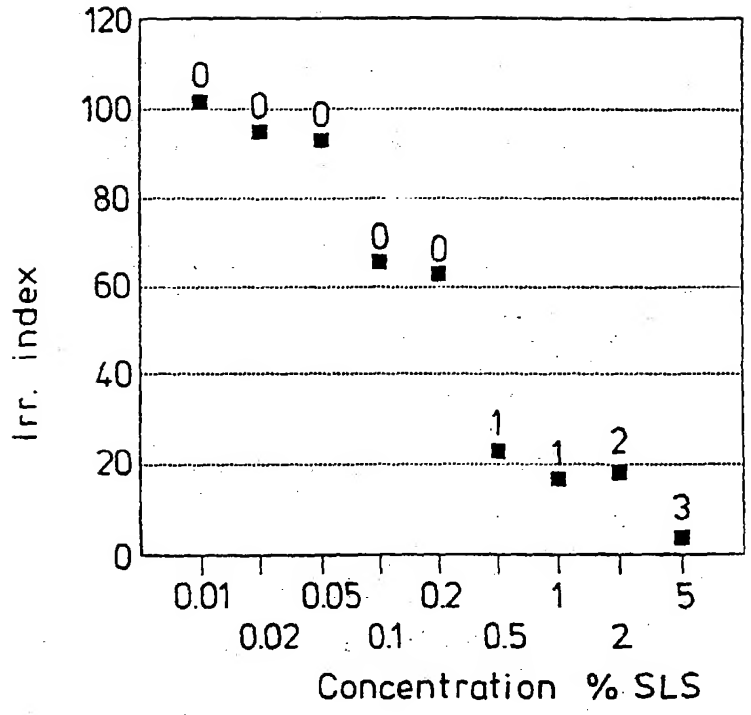
Minutes (SLS exp. between -30 and 0)

Fig. 7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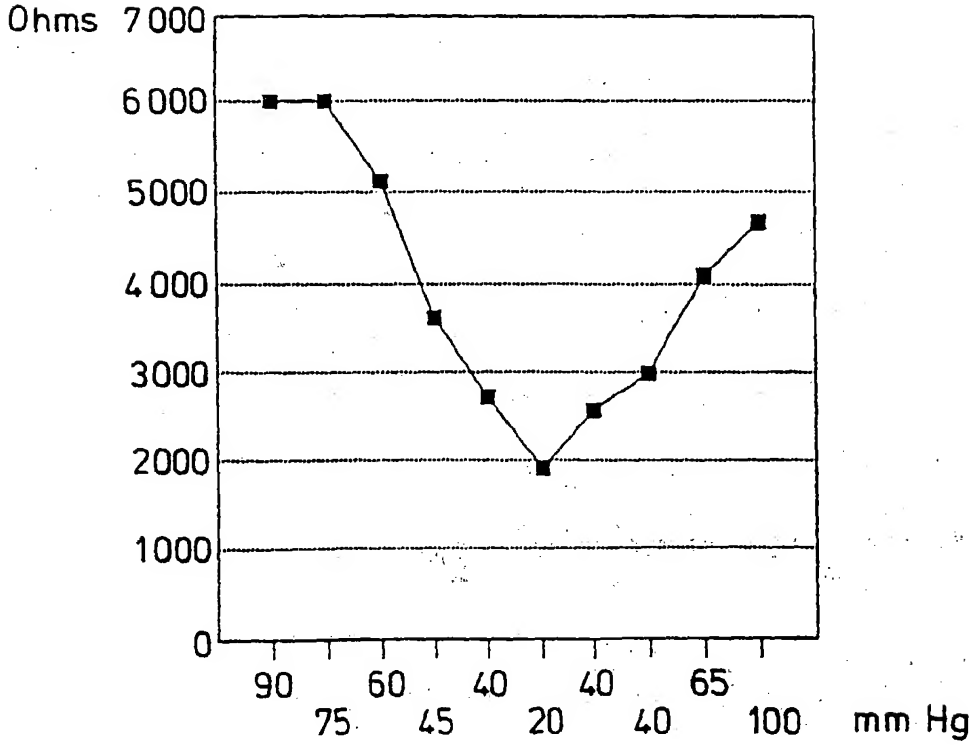
Concentration % SLS

Fig. 8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mm Hg

Fig. 9a

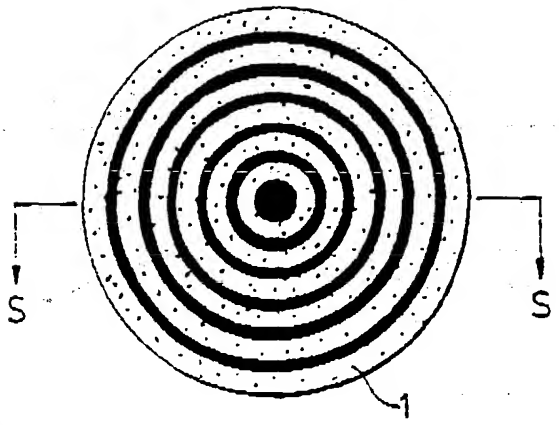
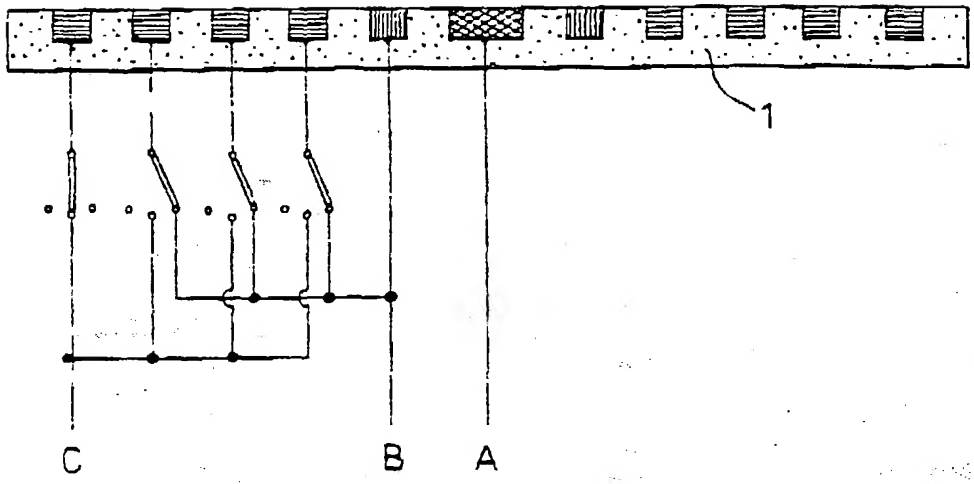


Fig. 9b

S-S



INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 91/00703

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 B 5/05

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	A 61 B

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP, A2, 0314088 (NIHON SYSTEM RESEARCH INSTITUTE INC.) 3 May 1989, see column 2, line 30 - column 3, line 18 --	1-18
X	EP, A1, 0315854 (KAO CORPORATION) 17 May 1989, see claim 3	18
A	--	1-17
A	US, A, 4540002 (D. ATLAS) 10 September 1985, see column 2, line 57 - line 61; column 5, line 29 - line 64 --	1-18
X	US, A, 4951683 (J.P. DAVIS) 28 August 1990, see claim 1	18
A	--	1-17
	--------	

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
14th January 1992	1992 -01- 20
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Anders Holmberg

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.PCT/SE 91/00703

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent Office EDP file on 30/11/91
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A2- 0314088	89-05-03	JP-A-	1113645	89-05-02
EP-A1- 0315854	89-05-17	JP-A-	1126535	89-05-18
		US-A-	4966158	90-10-30
US-A- 4540002	85-09-10	NONE		
US-A- 4951683	90-08-28	AU-D-	5026290	90-08-13
		CA-A-	2007903	90-07-19
		EP-A-	0429555	91-06-05
		JP-T-	3503971	91-09-05
		WO-A-	90/07902	90-07-26

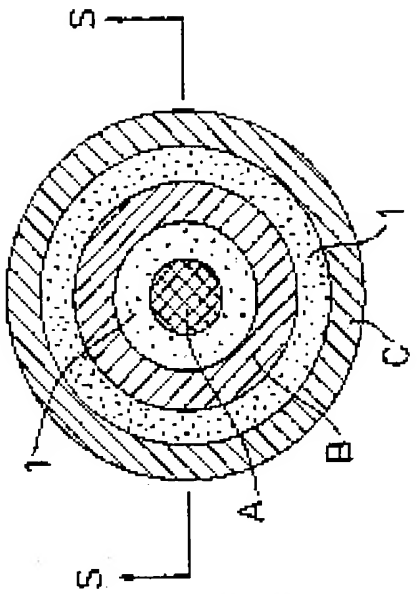


Fig. 2a

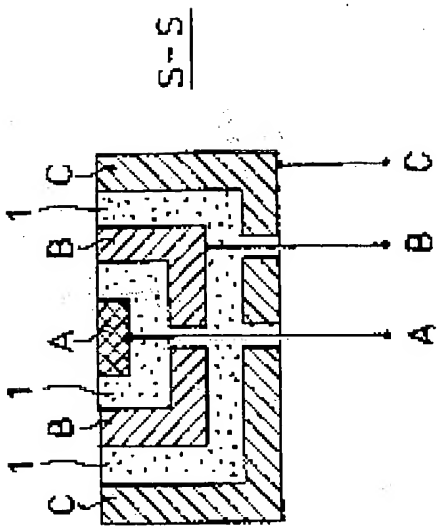


Fig. 2b

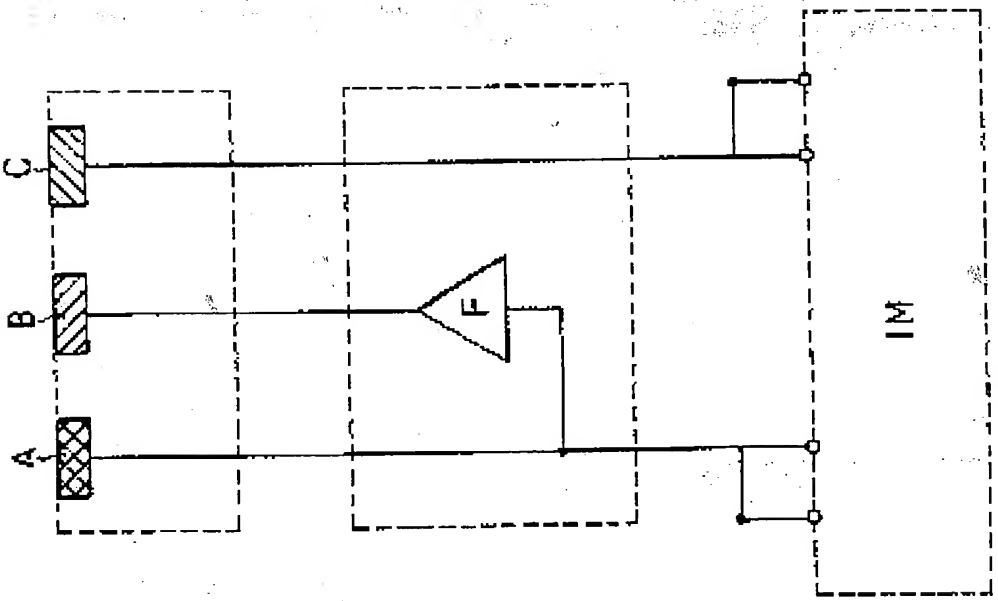


Fig. 1

Fig. 3a

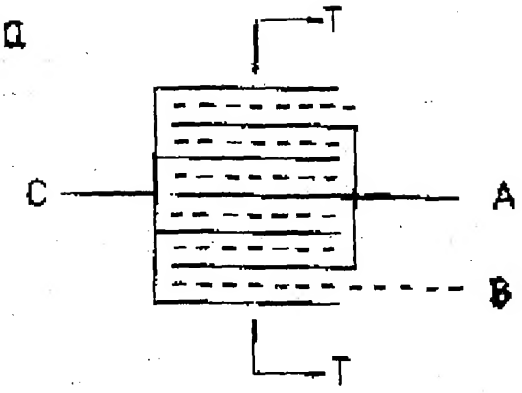
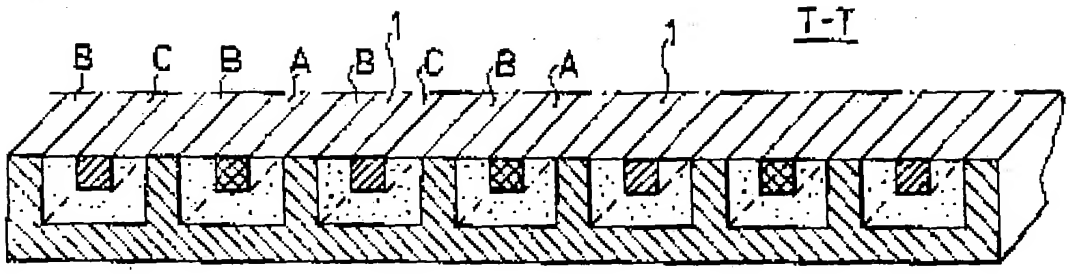


Fig. 3b



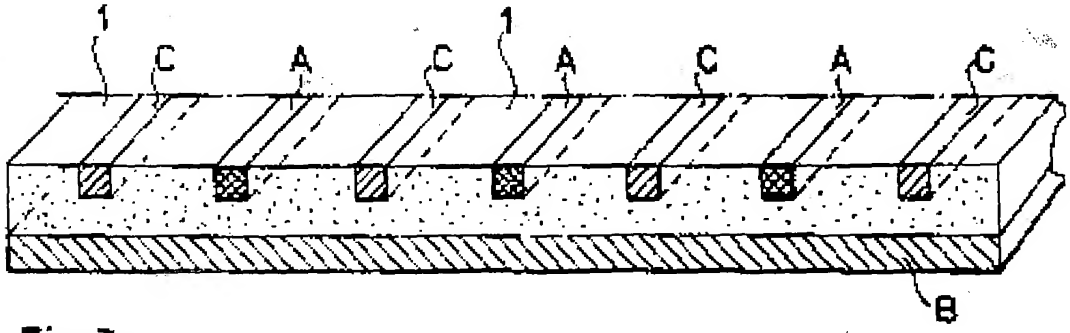


Fig. 3c

Fig. 4a

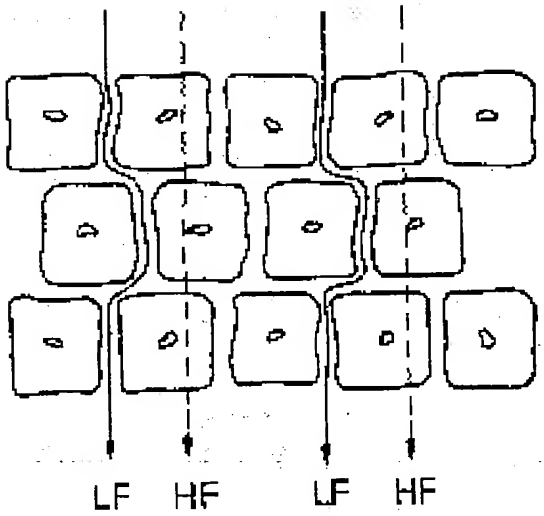


Fig. 4b

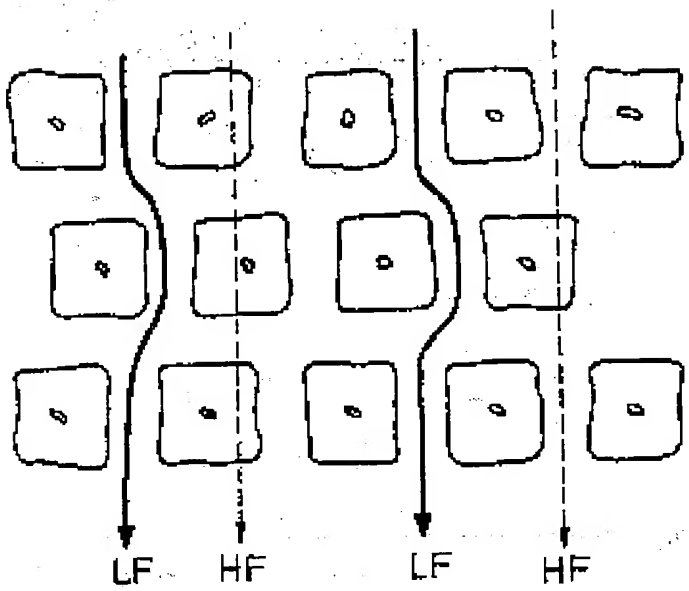
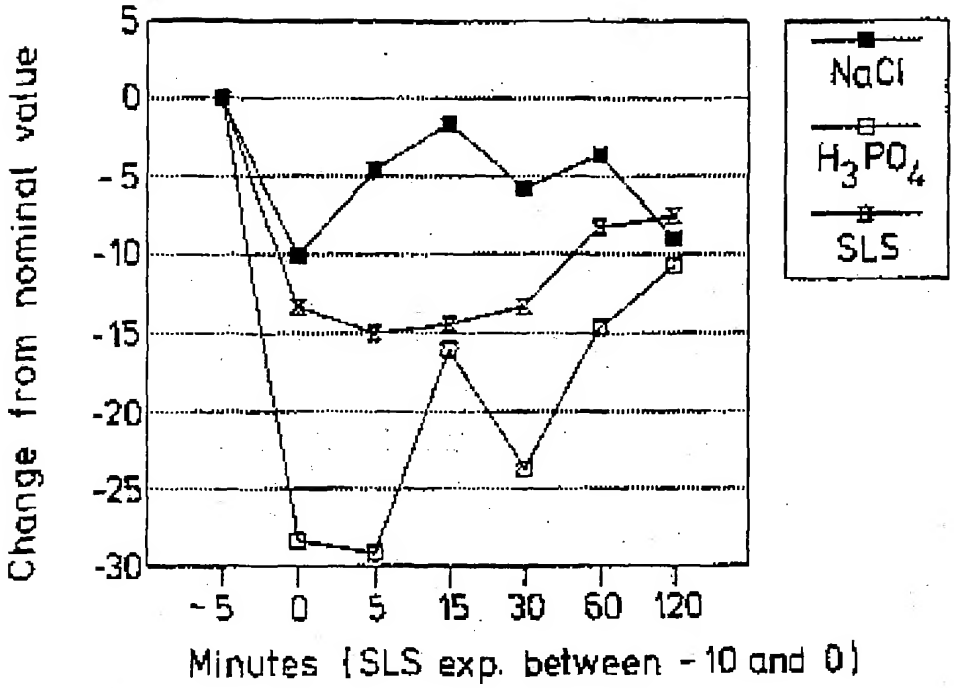


Fig. 5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H_3PO_4
SLS

Fig. 6

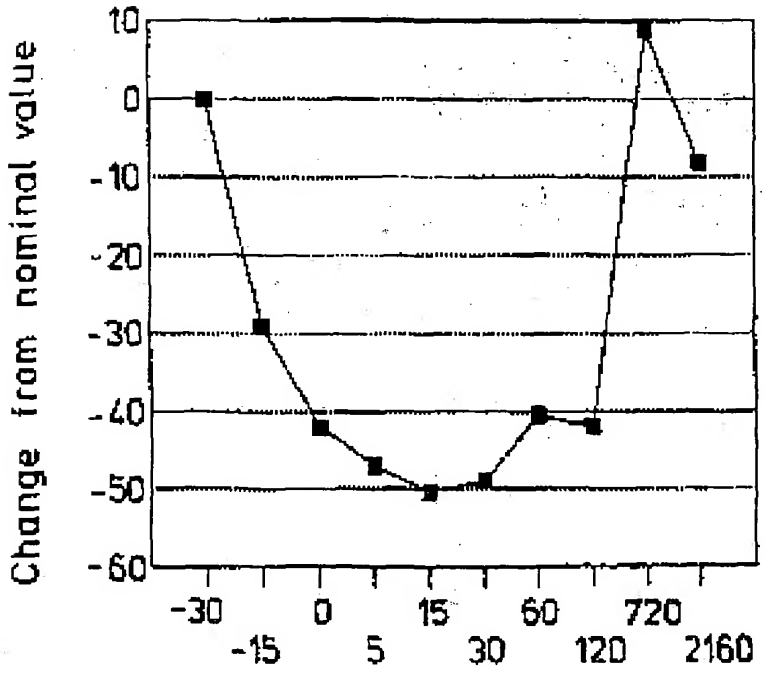
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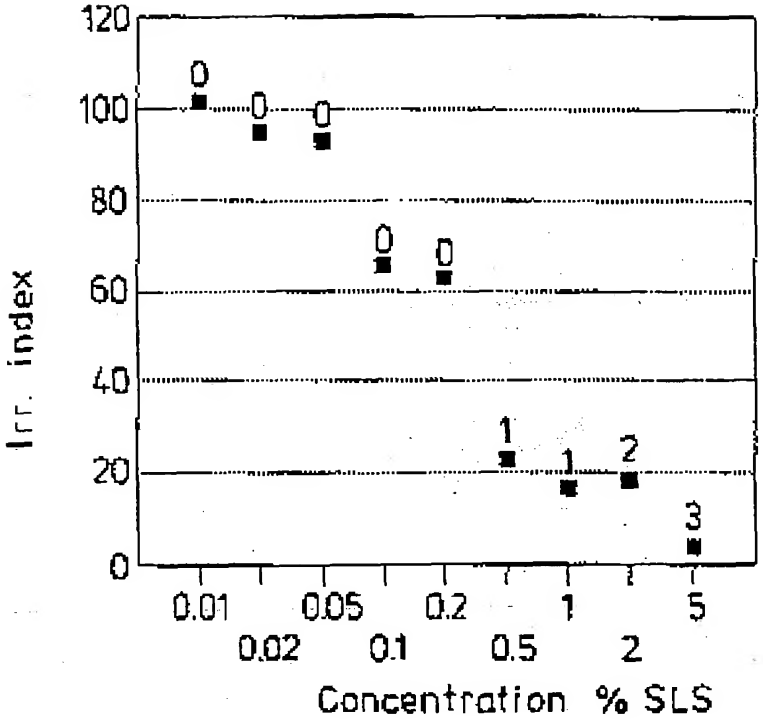
Fig. 7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Concentration % SLS

Fig. 8

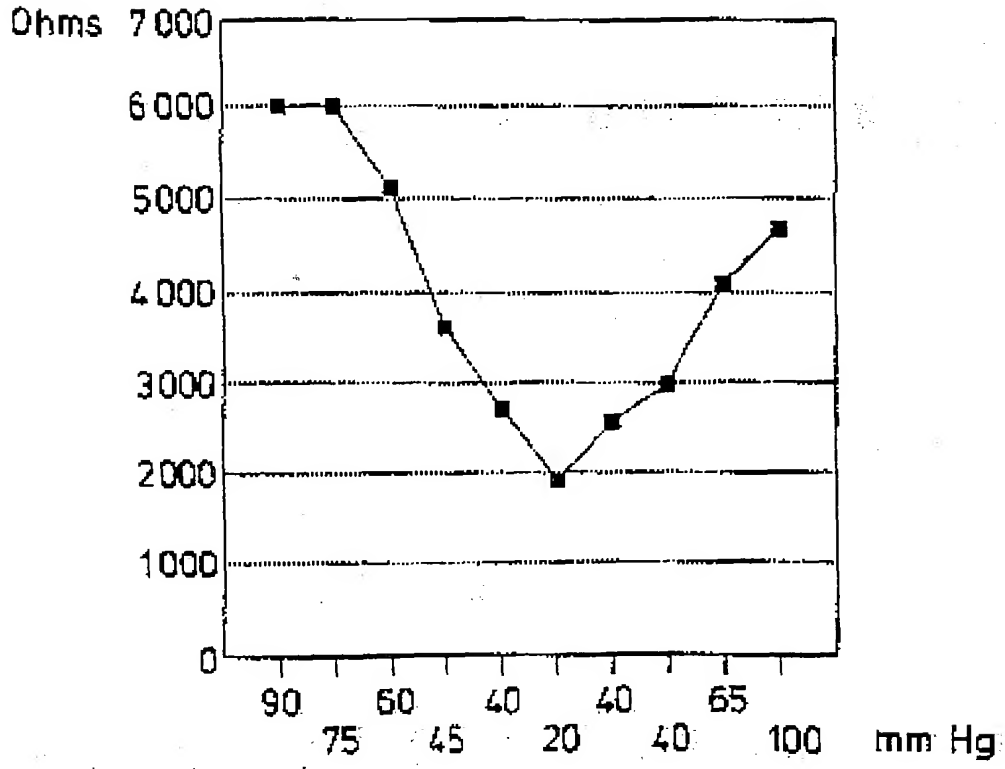
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Fig. 9a

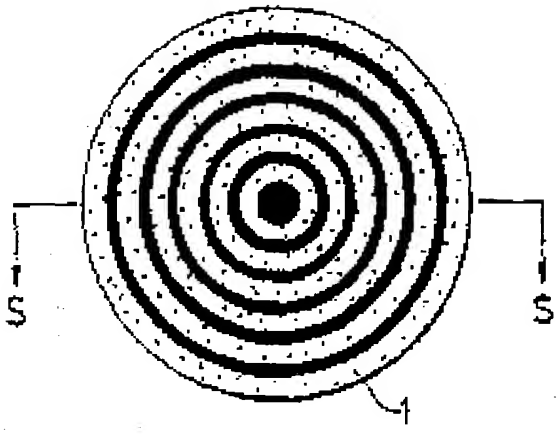

Fig. 9b

S-S